29 November 1973

Dr. Frank Rauscher
Director, National Cancer Institute
National Institutes of Health
Bethesda, Maryland 20014

Re: 2 RO1 AI 05160-16 (formerly CA 04496)
Genetics of Bacteria

Dear Dr. Rauscher:

As the time approaches for NCI consideration of this project, I thought it would be appropriate for me to submit some brief updating information, and some explicit arguments for the relevance of our work to your mission in cancer. Personally, I am sure you need little reminder on these points but it may be useful to have them on the record.

1. Much current thinking of the role of viruses in cancer stems in part from our past studies on the relationships between viruses and bacterial chromosomes. Transduction by viruses and the integration of the virus genome into the chromosome were discovered and experimentally corroborated in my laboratory (Zinder and Lederberg, 1952; Lederberg and Lederberg, 1951). Our initial work was done with bacteria and it is fair to refer to this as having been a path finder for contemporary studies with cancer cells along lines that I labored to encourage for many years.

2. You may know of an exciting breakthrough on splicing DNA molecules by procedures that exploit the specificities of restriction endonucleases. (Stanley Cohen, 1973). This is a somewhat different approach than enunciated in our proposal and it partly overlaps our own objectives. I have to point out that this result is based in large part on Dr. Sgaramella's observation in our laboratory that the restriction endonuclease leaves DNA strands with "sticky ends". In the competitive publication atmosphere that now prevails it is perhaps misleading that this critical point was mentioned only obliquely in a footnote.

Now that this additional procedure has been authenticated, together with the end to end joining of flush ended DNA by T4 ligase, we have even more powerful methods for pursuing our previous aims. We are in close communication with Dr. Cohen on these points and foresee no difficulty in proceeding on a cooperative basis.

3. For the review process it is unfortunate that the Division of Research Grants appears to have deleted the brief manuscript of which I again enclose a copy from the actual text of our proposal. We had intended to save considerable time and space by using this material directly rather than repeating it ad nauseum in a further verbal presentation. I have to mention this because some of the critical comment about our proposal which may have lead to a reduction in its priority rating had to do with what was asserted to be a somewhat sketchy account of our details and procedures. While this material was of course incorporated by reference, obviously it would have a much more limited impact on a busy review group than having the actual text in front of it. This inadvertence leads me to suggest that careful attention again be paid to the ways in which the mechanical procedures for the handling of the enormous load of scientific input in project proposals may influce their fair evaluation on scientific lines.

4. We have, since the preparation of that proposal, made substantial progress in the development of transection systems with phages P22 and T7. These lend themselves beautifully to further studies on the impact of incorporating new DNA sequences from other sources in the genetic function of these artificially reconstructed chromosomes. We are not necessarily confined to using DNA sources but can see ways of exploiting RNA inputs as well. This capability of transposing genetic informational sequences from various kinds of cells into bacteria and viruses opens up many new doors for diagnostic and therapeutic avenues in cancer. For the former it may well give a way to determine the informational changes that occur in different kinds of cancer cells. With respect to the latter, one can quite realistically think of using reconstructed bacterial or viral clones as ways of producing key cancer antigens and other critical substances.

5. I have to reiterate the urgency of timely funding as the only basis on which I can continue to sustain my laboratory work in molecular genetics. I realize that I may be more fortunate than some of my hard pressed colleagues in having other avenues of scientific work that I can continue to prosecute and I would certainly claim that these also have substantial scientific and social value. However, I would put the highest priority on a cost benefit basis for the work that I am doing in this arena at budgets that are relatively modest compared to many other programs. I believe that you will agree that it would be very much in the interest of further progress in cancer research to allow this to continue. This will not be possible if I do not receive positive word within the next few months as we are already operating on what amounts to a deficit basis.

Yours sincerely,

Joshua Lederberg
Professor and Chairman